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(54) **Propenyl amines, processes for their production and pharmaceutical compositions containing them.**

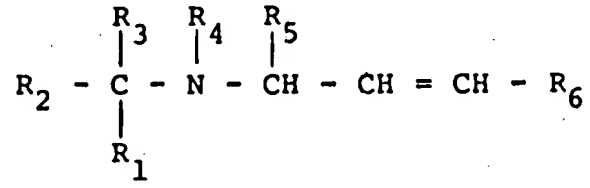
(57) The present invention provides propenylamines useful as anti-mycotic agents.

EP 0 000 896 A2

PROPENYL-AMINES, PROCESSES FOR THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

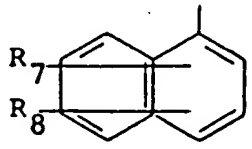
This invention relates to propenyl-amines, processes for their production and pharmaceutical compositions containing them.

The present invention provides a compound of formula I,



I

wherein a)(i) R_1 is a radical of formula IIa,



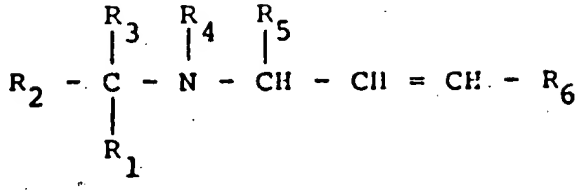
IIa

wherein R_7 and R_8, independently, are hydrogen, halogen of atomic number from 9 to 53, trifluoromethyl, hydroxy, nitro, lower alkyl or lower alkoxy,

or a radical of formula IIb, IIc, IId, IIe,

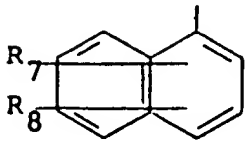
What is claimed:

1. A compound of formula I,



I

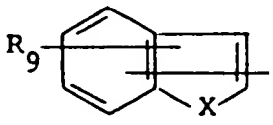
wherein a)(i) R_1 is a radical of formula IIa,

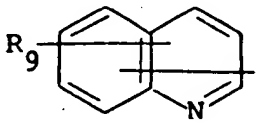


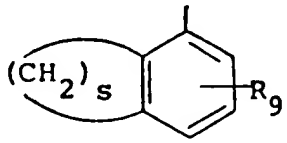
IIa

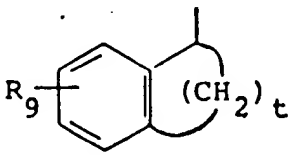
wherein R_7 and R_8, independently, are hydrogen, halogen of atomic number from 9 to 53, trifluoromethyl, hydroxy, nitro, lower alkyl or lower alkoxy,

or a radical of formula IIb, IIc, IId, IIe,


IIb


IIc


IId


IIe

wherein R_9 is hydrogen, halogen of atomic number from 9 to 53, hydroxy, lower alkyl or lower alkoxy,

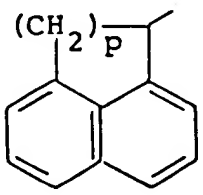
X is oxygen, sulphur, imino, lower alkylimino or a radical of formula $-(CH_2)_r-$ wherein r is 1, 2 or 3,

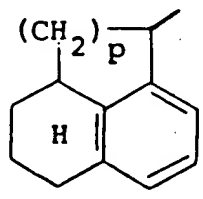
s is 3, 4 or 5, and

t is 2, 3 or 4, and

R_2 is hydrogen or lower alkyl, or

(ii) R_1 and R_2 together with the carbon atom to which they are bound form a radical of formula IIf or IIg,


IIf

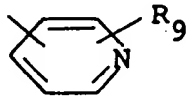

IIg

wherein p is 1, 2 or 3,

R_3 and R_5, independently, are hydrogen or lower alkyl,

R_4 is alkyl (C_{1-6}), alkenyl (C_{3-12}), alkynyl (C_{3-12}) or cycloalkyl (C_{3-8})-alkyl (C_{1-6}); and

R_6 is (i) an aromatic, five-membered heterocycle containing one oxygen, sulphur or nitrogen hetero-ring atom and optionally an additional one or two nitrogen hetero-ring atoms and being optionally substituted on a carbon ring atom by halogen of atomic number from 9 to 53, hydroxy, lower alkyl or lower alkoxy, and any nitrogen ring atom present being optionally substituted when possible, by lower alkyl, (ii) a radical of formula IIIa,



IIIa

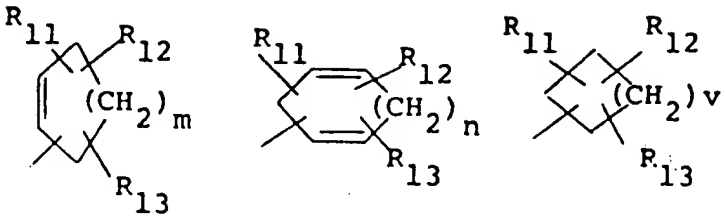
wherein R_9 is as defined above,

(iii) a radical of formula IIIb,

$$-CO-R_{10} \qquad \text{IIIb}$$

wherein R_{10} is alkyl (C_{1-12}), alkenyl (C_{3-12}), alkynyl (C_{3-12}) cycloalkyl (C_{3-8}) alkyl (C_{1-6}), phenyl-alkyl (C_{7-12}), phenyl, phenylalkoxy (C_{7-16}), or amino-alkyl (C_{1-12});

(iv) a radical of formula IIIc, IIId or IIIe,



IIIc IIId IIIe

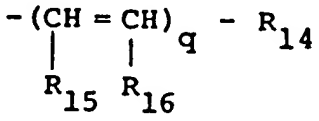
wherein R_{11}, R_{12} and R_{13}, independently, are hydrogen or lower alkyl,

m is a whole number from 0 to 4,

n is a whole number from 0 to 3, and

v is a whole number from 0 to 5,

(v) a radical of formula IIIf,

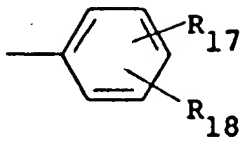


wherein R_{14} is lower alkyl, alkoxy (C_{1-12})-carbonyl, alkenyl (C_{3-12}), alkynyl (C_{3-12}), phenylalkyl (C_{7-12}) or phenyl,

R_{15} and R_{16}, independently, are hydrogen or lower alkyl, and

q is a whole number from 0 to 5, or

(vi) a radical of formula IIIg



IIIg

wherein R_{17} and R_{18}, independently, are hydrogen, halogen of atomic number from 9 to 53, trifluoromethyl, hydroxy, nitro, lower alkyl or lower alkoxy, with the proviso that one of R_{17} and R_{18} is other than hydrogen, and with the general proviso that R_1 is not a radical of formula IIa when R_6 is a radical of formula IIIg or phenyl, R_2 is hydrogen and R_3 is hydrogen or lower alkyl,

b) R_1 is a radical of formula IIa to IIe, as defined above,

R_2, R_5 and R_6 are as defined above, and

R_3 and R_4 together are $-(CH_2)_u-$ wherein u is a whole number from 1 to 8.

Any lower alkyl or lower alkoxy radical has preferably 1 to 4 carbon atoms, especially 2 or 1 carbon atoms. Any alkyl(C_{1-12}) moiety is preferably alkyl(C_{2-8}); phenylalkyl or phenylalkoxy has preferably 7 carbon atoms. Any alkenyl or alkynyl radical has preferably 3 to 6 carbon atoms, especially 3 or 4 carbon atoms. Preferably the multiple bond is in other than the α, β position and is conveniently in the remote terminal position. An example of an alkenyl group is allyl. An example of an alkynyl group is

propinyl. Cycloalkylalkyl has preferably an alkyl moiety of 1 to 4 carbon atoms, especially 2 or 1 carbon atoms, and a cycloalkyl moiety preferably of 3 to 6 carbon atoms. When R_4 is cycloalkylalkyl this is especially cyclopentyl alkyl or cyclohexylalkyl. When R_{10} is cycloalkylalkyl this is especially cyclopropylalkyl or cyclobutylalkyl.

Conveniently R_7 and R_8 are identical and are both hydrogen. Conveniently R_9 is hydrogen or halogen. In IIb and IIc the bond to the carbon atom to which R_2 and R_3 are attached is conveniently attached meta to X and para to the ring nitrogen, respectively. X is conveniently sulphur, imino or lower alkylamino. R_1 is preferably a radical of formula IIb, IIc or IId or especially IIa. ———— ———— R_2 is preferably hydrogen. R_3 is preferably hydrogen and R_4 is conveniently alkyl. R_5 is conveniently hydrogen. R_6, when it is a heterocycle, conveniently contains one oxygen or sulphur atom or one or two nitrogen atoms. Preferably the bond linking R_6 to the vinylene moiety is attached to a ring carbon atom adjacent to a ring heteroatom. Conveniently the ring is unsubstituted or substituted by lower alkyl. R_{10} is conveniently phenylalkoxy. IIa is conveniently optionally substituted 2 or 4-pyridyl. In IIIc, IIId, IIIe it is to be appreciated that the bond linking R_6 to the vinylene moiety and R_{11} to R_{13} may be attached to any of the ring carbon atoms present. IIIc is preferably a cycloalk-1-en-1-yl radical. Preferably R_{11} to R_{13} are hydrogen. q is conveniently 0 or 1.

Any double bond in IIIf is conveniently trans. R_{14} is conveniently alkoxy (C_{1-8}) carbonyl, phenyl or alkyl or phenalkyl. R_{17} is conveniently halogen and R_{18} is conveniently hydrogen. R_6 is conveniently IIIc. u is conveniently 3, 4 or 5, more conveniently 4.

The values m, n, p, q, s, t and v are conveniently chosen to produce a five or six-membered ring.

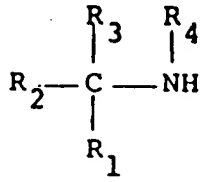
The double bond between R_6 and the nitrogen atom preferably has the trans configuration.

Halogen is conveniently fluorine, or preferably bromine or chlorine.

When R_1 is IIb or IIe and R_6 is IIIa it is to be appreciated that the two radicals R_9 may be the same or different.

The present invention also provides a process for the production of a compound of formula I, which comprises

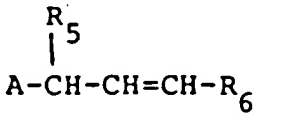
a) reacting a compound of formula IV,



IV

wherein R_1 to R_4 are as defined above,

with a compound of formula V,

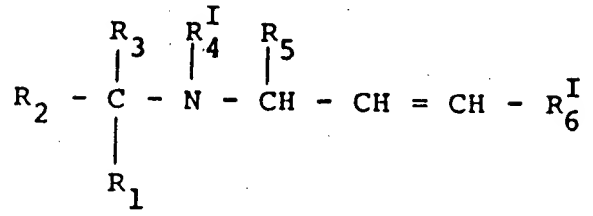


V

wherein A is a leaving group, and

R_5 and R_6 are as defined above, or

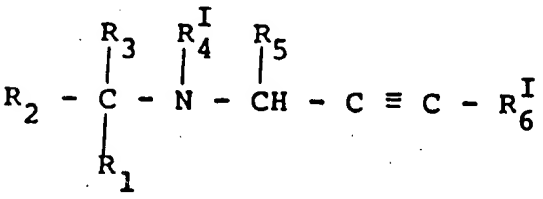
b) producing a compound of formula Ia,



Ia

wherein R_1 to R_3 and R_5 are as defined above, and R_4^I and R_6^I are as defined above for R_4 and R_6 respectively, with the proviso that they each are other than alkynyl,

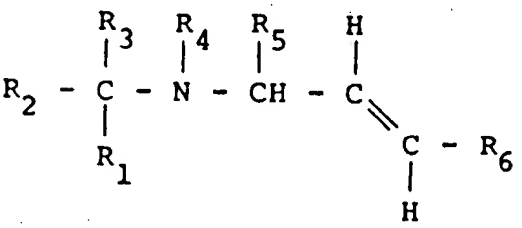
by reducing a compound of formula VI,



VI

wherein R_1 to R_3, R_4^I, R_5 and R_6^I are as defined above, or

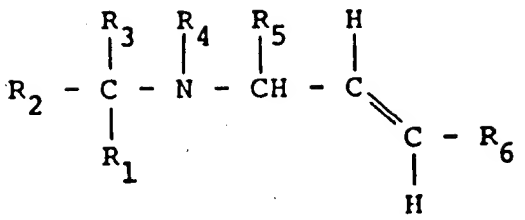
c) producing a compound of formula Ib,



Ib

wherein R_1 to R_6 are as defined above,

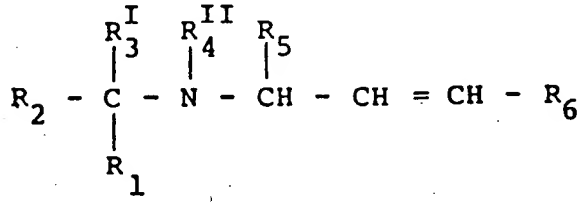
by isomerising photochemically a compound of formula Ic,



Ic

wherein R_1 to R_6 are as defined above, or

d) producing a compound of formula Id,



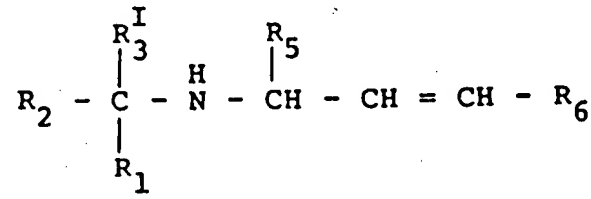
Id

wherein R_1, R_2, R_5 and R_6 are as defined above,

R_3^I is hydrogen or lower alkyl,

R_4^{II} is alkyl(C_{1-6}), alkenyl(C_{3-12}), alkynyl (C_{3-12}) or cycloalkyl(C_{3-8})alkyl(C_{1-6});

by introducing the group R_4^{II} into a compound of formula VII,



VII

wherein R_1, R_2, R_3^I, R_5 and R_6 are as defined above.

Process a) may be effected in conventional manner for the production of tertiary amines by condensation from analogous starting materials. The process may be effected in an inert solvent such as a lower alkanol, e.g. ethanol,

optionally in aqueous admixture, an aromatic hydrocarbon solvent, e.g. benzene or toluene, a cyclic ether, e.g. dioxane or a carboxylic acid dialkylamide solvent, e.g. dimethylformamide. The reaction temperature is conveniently from room temperature to the boiling temperature of the reaction mixture, preferably room temperature. The reaction is conveniently effected in the presence of an acid binding agent, such as an alkali metal carbonate, e.g. sodium carbonate. The leaving group A is conveniently iodine or preferably chlorine or bromine, or an organic sulphonyloxy group having 1 to 10 carbon atoms, e.g. alkylsulphonyloxy, preferably having 1 to 4 carbon atoms such as mesyloxy, or alkylphenylsulphonyloxy preferably having 7 to 10 carbon atoms such as tosyloxy.

Process b) may be effected in conventional manner for catalytic hydrogenation in order to produce a compound of formula Ia wherein the double bond adjacent to R_6^I has the cis configuration. Alternatively, the process may be effected in conventional manner for a complex metal hydride reduction in order to produce a compound of formula Ia wherein the double bond has the trans configuration.

The catalytic hydrogenation may be effected in a solvent, e.g. methanol, ethanol, methylene chloride, pyridine or ethyl acetate. The catalyst is preferably palladium on a carrier material such as $BaSO_4$ or $CaCO_3$. The catalyst

may be pretreated, e.g. with a lead salt, so as to be partially poisoned (e.g. a Lindlar catalyst). The hydrogenation may be effected at room temperature and at normal pressure.

The metal hydride reduction may be effected in conventional manner for a lithium aluminium hydride or a diisobutylaluminium hydride reduction. The reduction is conveniently effected in an inert solvent such as toluene or benzene. The reaction is conveniently effected at room temperature.

Process c) may be effected in conventional manner for a photochemical isomerisation of a cis alkene. The reaction may be effected in a solvent such as benzene, petroleum ether, ethanol, or preferably cyclohexane. The solution is conveniently irradiated with light from a mercury high or low pressure lamp. The reaction is conveniently effected at room temperature. If desired, an appropriate sensitizer such as eosine or a catalyst such as diphenyldisulphide may be present.

Process d) may be effected in manner conventional for the "alkylation" of secondary amines (the term "alkylation" being used here to denote introduction of any of the hydrocarbyl groups R_4^{II}), for example by direct "alkylation" with an "alkylating" agent, for example a halide or sulphate,

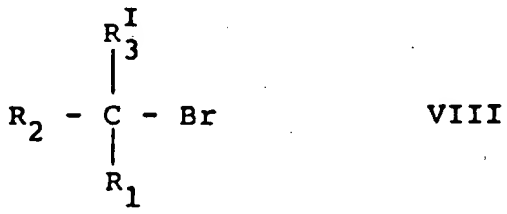
or by reductive alkylation, in particular by reaction with an appropriate aldehyde and subsequent or simultaneous reduction. Reductive "alkylation" is suitably effected in an inert organic solvent, such as a lower alkanol, e.g. methanol, and at an elevated temperature, in particular at the boiling temperature of the reaction medium. The subsequent reduction may be effected with, for example, a complex metal hydride reducing agent, e.g. $NaBH_4$ or $LiAlH_4$. The reduction may also be effected simultaneously to the alkylation, for example by use of formic acid which may serve both as reducing agent and as a reaction medium.

It is to be appreciated that in any of the above processes, side reactions may occur, e.g. reduction of halogen to hydrogen, reduction of a nitro group to an amino group, reduction of an alkenyl moiety to an alkyl moiety and/or reduction of a keto moiety to a carbinol moiety in processes b) or process d) when reductive alkylation is used, or simultaneous cis/trans isomerisation of any double bond present in R_4 or R_6 when process c) is used. The reaction conditions should be chosen to avoid such side reactions, and the desired final product isolated using conventional purification techniques, e.g. thin layer chromatography.

Free base forms of the compounds of formula I may be converted into salt forms and vice versa. Suitable acids

for acid addition salt formation include hydrochloric acid, fumaric acid and naphthalene-1,5-disulphonic acid.

The starting materials are either known or may be made in conventional manner. For example non-cyclic amines of formula IV may be made by condensing a compound of formula VIII,

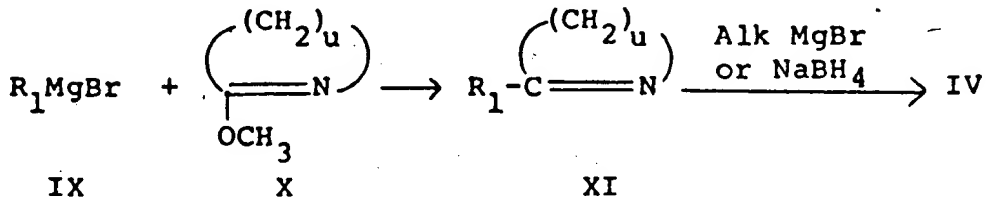


VIII

or the corresponding iodide or chloride,

with a compound of formula $R_4^{II}NH_2$.

The cyclic amines of formula IV may be made as follows:-

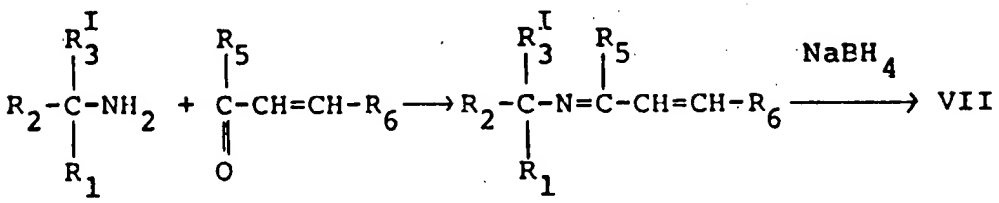


IX X XI

wherein Alk = lower alkyl.

The compounds of formula VI are new and may be made by reacting an appropriate amine of formula IV with compounds of formulae R_5-CHO and $HC \equiv CR_6^I$ under Mannich reaction conditions.

The compounds of formula VII are also new and may be made as follows:-



In the following Examples all temperatures are uncorrected and in degrees Centigrade.

In the tables hereinafter, the following indications are used:-

1) All double bonds have the trans configuration; all alkyl groups are unbranched unless stated otherwise.

2) If no melting point is given, the free base form of the compound is obtained and this is an oil. Melting points are for the free base form unless specified otherwise.

3) Monohydrochloride salt form.

4) Dihydrochloride salt form.

EXAMPLE 1: 4-[N-methyl-N-(1-naphthylmethyl)]aminocrotonic acid ethyl ester [process a)]

1.9 g of bromocrotonic acid ethyl ester are added dropwise to a mixture of 1.7 g of N-methyl-N-(1-naphthylmethyl)amine, 1.4 g of K_2CO_3 and 10 ml dimethylformamide. After the mixture is stirred for 18 hours at room temperature, it is filtered and evaporated under a vacuum. The residue is chromatographed on silica-gel using benzene/ethyl acetate (1:1) as solvent to yield the title compound in free base form, as an oil, after evaporating the appropriate fractions.

The title compound may also be made in analogous manner to Examples 3, 4 and 5.

EXAMPLE 2: N-(3-cyclohex-1-en-1-yl-2-cis-propenyl)-N-methyl-N-(1-naphthylmethyl)amine [process b)]

5 g of N-(3-cyclohex-1-en-1-yl-propynyl)-N-methyl-N-(1-naphthylmethyl)amine are hydrogenated in absolute pyridine using 750 mg $Pd/BaSO_4$ as catalyst at room temperature and normal pressure, until the calculated amount of hydrogen is taken up. The reaction mixture is filtered and the pyridine removed in a vacuum. The residue is chromatographed on silica-gel using benzene/ethylacetate (9:1) to yield the title compound in free base form as an oil after evaporating the appropriate fractions,

m.p. (Hydrochloride) 184-188°.

The title compound may also be made in analogous manner to Examples 1 and 5.

EXAMPLE 3: N-(3-cyclohexyl-2-trans-propenyl)-N-methyl-N-(1-naphthylmethyl)amine [process b)]

28 ml of a 1.2 molar solution of diisobutylaluminium hydride in toluene are added to 5 g of N-(3-cyclohexyl-propynyl)-N-methyl-N-(1-naphthylmethyl)amine in absolute benzene. After the mixture is stirred for 3 hours at 40°, water is carefully added. The organic phase is separated off, dried and evaporated to yield the title compound in free base form, as an oil.

The title compound may also be prepared by following Examples 1, 4 and 5.

EXAMPLE 4: N-(3-cyclohex-1-en-1-yl-2-trans-propenyl)-N-methyl-N-(1-naphthylmethyl)amine [process c)]

1.2 g of N-(3-cyclohex-1-en-1-yl-2-cis-propenyl)-N-methyl-N-(1-naphthylmethyl)amine are irradiated for 3 hours with a Hg high pressure lamp ($\lambda > 300$ nm) in 1 litre cyclohexane in the presence of 50 mg diphenyldisulphide at room temperature under an inert gas atmosphere. After the solvent is evaporated, the title compound is obtained in free base form and converted into the hydrochloride, m.p.

184-188°

The title compound may also be prepared by following Examples1, 3 and 5.

EXAMPLE 5: N-methyl-N-[3-(5'-methyl-2'-thienyl)-2-trans-propenyl)-N-(1-naphthylmethyl)amine [process d)]

a) 15.2 g of 3-(5'-methyl-2'-thienyl)prop-2-enal and 15.7 g of 1-aminomethylnaphthalene in 350 ml benzene are boiled under reflux until the calculated amount of water has boiled off. 3.6 g of the resulting Schiff base in 100 ml methanol are boiled under reflux with 5 g $NaBH_4$ for 30 minutes to yield N-[3-(5'-methyl-2'-thienyl)-2-trans-propenyl)]-N-(1-naphthylmethyl)amine, which is used directly in the next stage. [To isolate this intermediate the reaction mixture is evaporated in a vacuum; the residue is partitioned between aqueous sodium carbonate solution and diethyl ether and the organic phase is evaporated].

b) The crude reaction mixture obtained in step a) is treated with 20 ml 37% aqueous formaldehyde solution. The mixture is boiled under reflux for 60 minutes, subjected to ice-cooling, treated with 9 g $NaBH_4$ and stirred for another 60 minutes at room temperature. The mixture is evaporated in a vacuum to a residue which is partitioned between aqueous $NaHCO_3$ and diethyl ether. The organic phase is dried and evaporated

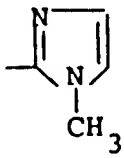
to yield the title compound in free base form as an oil, m.p. (hydrochloride) 140-156°.

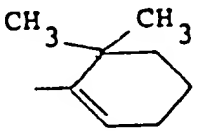
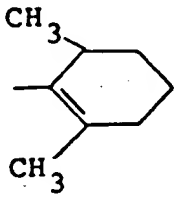
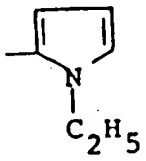
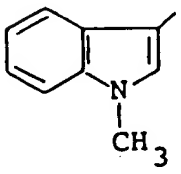
The title compound may also be prepared in analogous manner to Examples 1, 3 and 4.

In analogous manner to that described in Examples 1, 3, 4 and 5, the following trans compounds of formula Ie may be produced:

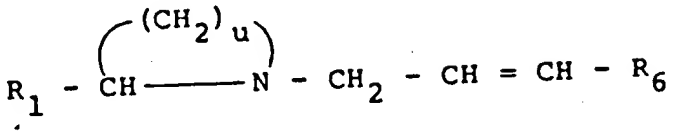
$R_1-CH_2-N(CH_3)-CH_2-CH=CHR_6$ Ie

wherein R_1 and R_6 are as follows:

Ex.	R_1	R_6 [1]	m.p. [2]
6	1-naphthyl	$-COOC_5H_{11}$	
7	1-naphthyl	$-COOC_8H_{17}$	
8	1-naphthyl	$-COOCH_2C_6H_5$	
9	1-naphthyl	2-thienyl	182-187 [3]
10	1-naphthyl	2-furyl	
11	1-naphthyl		175-185 [4]
12	1-naphthyl	Cyclohex-3-en-1-yl	
13	1-naphthyl	2-pyridyl	
14	1-naphthyl	3-pyridyl	
15	1-naphthyl	4-pyridyl	174-178 [4]
16	1-naphthyl	$-CH=CH.C_6H_5$	170-174 [3]

Ex.	R_1	R_6 [1]	m.p. [2]
17	1-naphthyl	$-CH=CH.C_4H_9$	
18	1-naphthyl	2-pyrrolyl	
19	1-naphthyl	Cyclohept-1-en-1-yl	193-196 [3]
20	1-naphthyl	Cyclopent-1-en-1-yl	
21	1-naphthyl		180-184 [3]
22	1-naphthyl	$-CH=CH-COOC_2H_5$	
23	1-tetralinyl	C_6H_5	
24	1-tetralinyl	Cyclohex-1-en-1-yl	
25	5-tetralinyl	C_6H_5	
26	4-quinolyl	C_6H_5	
27	3-benzo[b]thienyl	C_6H_5	
28	3-benzo[b]thienyl	Cyclohex-1-en-1-yl	175-177 [3]
29	1-naphthyl		
30	1-naphthyl		
31		C_6H_5	

In analogous manner to that described above for Examples 1, 3 and 4 there may be produced the following trans compounds of formula If,



If

wherein R_1, R_6 and u are as follows:

Ex.	R_1	R_6 [1]	u	m.p. [2]
32	1-naphthyl	C_6H_5	4	203-205 [3]
33	1-naphthyl	C_6H_5	3	75-78
34	1-naphthyl	C_6H_5	5	171-175 [3]
35	1-naphthyl	$COOC_5H_{11}$	4	
36	1-naphthyl	C_6H_5	1	
37	1-naphthyl	Cyclohex-1-en-1-yl	4	
38	1-naphthyl	4-F-C_6H_4	4	
39	1-naphthyl	3-pyridyl	4	
40	3-benzo[b]thienyl	C_6H_5	4	
41	5-tetralinyl	C_6H_5	4	150-155 [3]

EXAMPLE 42:

In analogous manner to that described in Examples 1 and 2, the following cis compound of formula I may be produced:

aa) N-(3-cyclohex-1-en-1-yl-2-cis-propenyl)-2-(1'-naphthyl)-piperidine ; free base-oil.

EXAMPLES 43-47:

In analogous manner to that described in Examples 1, 3, 4 and 5, the following compounds of formula I may be produced:

43) N-cinnamyl-N-methyl-N-[2-(1'-naphthyl)-2-propyl]amine; free base-oil;

44) N-(1-acenaphthenyl)-N-methyl-N-(3-phenyl-2-trans-propenyl)amine, m.p. (hydrochloride) 210-216°;

45) N-(1-acenaphthenyl)-N-methyl-N-[3-(5'-methyl-2'-thienyl)-2-trans-propenyl)amine, free base-oil;

46) N-(6,7,8,8a-tetrahydro-1-acenaphthenyl)-N-methyl-N-(3-phenyl-2-trans-propenyl)amine, m.p. (hydrochloride) 185-192°;

47) N-methyl-N-(2,3-dihydro-1-phenalenyl)-N-(3-phenyl-2-trans-propenyl), free base-oil.

NMR data on the above-mentioned compounds of formula I, obtained as oils, are given in the following table. The data comprises peak position in ppm relative to TMS as standard in $CDCl_3$; type of peak (D = doublet; DD = double

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doublet; DT = double triplet; M = multiplet; Q = quartet; S = singlet; T = triplet) and in parentheses the corresponding number of hydrogen atoms.

Ex.	NMR Data
1	1.2 T (3); 2.25 S (3); 3.2 M (2); 3.9 S (2); 4.2 Q (2); 6.0 D (1); 6.85 - 7.2 M (1); 7.3 - 7.9 M (6); 8.2 (1).
3	0.8 - 2.2 (11); 2.2 S (3); 3.0 M (2); 3.85 S (2); 5.6 M (2); 7.3 - 7.9 (6); 8.3 M (1)
6	0.7 - 1.8 M (9); 2.25 S (3); 3.2 M (2); 3.9 S (2) 4.1 T (2); 6.0 D (1); 6.9 - 7.2 M (1); 7.3 - 7.9 M (6); 8.3 M (1); 4.1 T (2).
7	0.8 - 1.8 M (15); 2.3 S (3); 3.25 M (2); 3.95 S (1); 4.1 T (2); 6.0 M (1); 6.9 - 7.2 M (1); 7.4 -7.9 M (6); 8.2 - 8.4 M (1)
8	2.3 S (3); 3.2 M (2); 3.9 S (2); 5.15 S (2); 6.1 M (1); 6.9 - 7.9 M (13); 8.2 - 8.4 M (1).
10	2.28 S (3); 3.28 T (2); 3.94 S (2); 6.25 M (4); 7.42 M
12	1 - 2.5 M (7); 2.2 S (3); 3.0 M (2); 3.85 S (2); 6.4 - 6.8 M (4); 7.2 - 7.9 (6); 8.2 - 8.4 M (1).
13	2.3 S (3); 3.35 D (2); 4.0 S (2); 7.0 - 8.0 M (9); 8.2 - 8.4 M (1); 8.55 M (1)
14	2.3 S (3); 3.25 D (2); 3.95 S (2); 6.2 - 6.7 M (2); 7.0 - 7.8 M (8); 8.2 - 8.7 M (3)

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Ex.	NMR Data
17	0.8 - 1.5 (7); 3.0 - 3.3 M (2); 3.2 S (3); 3.15 D (2); 3.9 S (2); 5.5 - 6.4 M (4); 7.2 - 8.4 (7).
18	2.26 S (3); 3.22 D (2); 3.94 S (2); 5.85 DT; 6.18 M (2); 6.45 D (1); 6.74 M (1); 7.4 - 8.5 M (6); 8.3 M (1)
20	1.7 - 2.1 (2); 2.2 - 2.6 (4); 2.2 S (3); 3.15 D (2); 3.86 S (2); 5.5 - 5.85 M (2); 6.45 D (1); 7.2 - 7.9 (6); 8.3 M (1).
22	1.28 T (3); 2.24 S (3); 3.2 D (2); 3.9 S (2); 4.2 Q (2); 5.84 D (1); 6.2 - 6.5 M (2); 7.2 - 7.9 (7); 8.2 - 8.3 M (1)
23	1.6 - 1.9 M (4); 2.2 S (3); 2.7 - 2.9 M (4); 3.2 D (2); 3.45 S (2); 6.1 - 6.7 M (2); 6.9 - 7.5 (8)
24	1.4 - 1.9 (8); 2.0 - 2.3 (4); 2.17 S (3); 2.8 M (4); 3.06 D (2); 3.4 S (2); 5.4 - 5.8 (2); 6.16 D (1); 6.9 - 7.2 (4)
25	1.6 - 2.1 M (4); 2.35 S (3); 2.2 - 3.4 M (7); 6.0 - 6.6 M (2); 7.0 - 7.4 M (9)
26	2.3 S (3); 3.25 D (2); 3.9 S (2); 6.2 - 6.7 M (2); 7.1 - 7.8 (9); 8.2 M (2); 8.85 D (1)
27	2.3 S (3); 3.25 D (2); 3.8 S (2); 6.2 - 6.7 M (2); 7.2 - 7.5 (8); 7.8 - 8.0 M (2)
29	1.1 D (3); 1.3 - 2.8 (7); 1.75 S (3); 2.25 S (3); 3.25 D (2); 3.91 M (2); 5.8 DT (1); 6.5 D (1); 7.3 - 7.9 (6); 8.3 M (1)

Ex.	NMR Data
30	1.33 T (3); 2.27 S (3); 3.26 D (2); 3.91 Q (2); 3.94 S (2); 6.0 - 6.7 M (5); 7.3 - 7.7 M (4); 7.7 - 7.9 M (2); 8.3 M (1);
31	2.28 S (3); 3.02 S (3); 3.18 D (2); 3.86 S (2); 6.2 - 6.6 M (2); 6.65 (1); 7.0 - 7.4 M (8); 8.0 M (1)
35	2.5 - 2.8 DD (1); 3.1 - 3.5 M (3); 3.8 - 4.0 M (1); 4.1 T (2); 5.9 D (1); 6.7 - 7.05 M (1); 7.3 - 8.0 M (6); 8.5 M (1)
36	1.9 - 2.1 M (2); 2.95 - 3.1 M (1); 3.4 D (1); 6.2 - 6.8 M (2); 7.0 - 8.4 (12);
37	2.4 - 2.7 DD (1); 3.0 - 3.5 M (3); 3.7 - 4.0 (1); 5.2 - 5.6 M (3); 5.9 D (J = 16Hz) (1); 7.3 - 8.0 (6); 8.3 - 8.8 (1)
38	1.3 - 2.4 M (7); 2.65 DD (1); 3.15 - 3.25 M (2); 3.65 - 3.95 (1); 5.8 - 6.4 (2); 6.8 - 7.9 (10); 8.3 - 8.8 broad S (1)
39	1.2 - 2.8 (8); 3.15 - 3.45 (2); 3.8 - 4.0 (1); 6.2 M (2); 7.0 - 7.9 (8); 8.2 - 8.6 (3);
40	1.2 - 2.4 (7); 2.6 - 2.85 DD; 3.15 - 3.8 (3); 6.1 - 6.8 (2); 7.1 - 7.6 (8); 7.8 - 7.9 M (1); 8.15 - 8.25 M (1)
42	2.8 - 3.1 DD (1); 3.1 - 3.5 M (3); 3.7 - 4.0 (1); 5.2 - 5.6 M (3); 5.8 D (J = 13Hz) (1); 7.3 - 8.0 (6); 8.3 - 8.8 (1)

Ex.	NMR Data
43	1.62 S (6); 2.34 S (3); 3.15 D (2); 6.03 DT (1); 6.40 D (1); 7.1 - 7.9 (11); 9.55 M (1)
45	2.18 S (3); 2.40 S (3); 3.20 M (4); 4.95 M (1); 6.50 M; 7.40 M
47	2.38 S (3); 3.30 M (4); 4.20 M (1); 6.35 M (2); 7.30 M (11)

The compounds of formula I exhibit chemotherapeutic activity. In particular, they exhibit antimycotic activity, as indicated in vitro with tests against various families and types of mycetes, including Trichophton quinkeanum, Aspergillus fumigatus, Microsporum canis, Sporotrychium schenkii and Candida albicans, at concentrations of, for example 0.1 to 100 µg/ml, and in vivo in the experimental skin mycosis model in guinea pigs. In the latter model, guinea pigs are infected by cutaneous application of Trichophyton quinkeanum. The test substance is administered daily for 7 days beginning 24 hours after the infection by local application by rubbing the test substance (taken up in polyethylene glycol) on the skin surface, or perorally, the test substance being administered as a suspension. The activity is shown on local application at concentrations of from example 0.1 to 2%, in particular 0.1 to 0.6%. The oral activity is shown at dosages of, for example, 50 to 100 mg/kg.

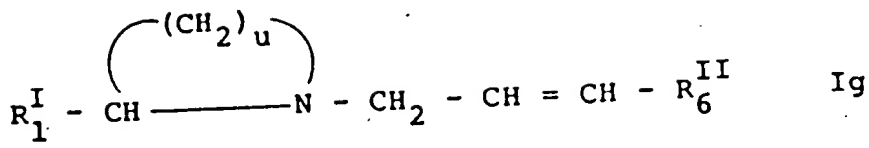
The compounds are therefore indicated for use as anti-mycotic agents. An indicated daily dose is from 500 to 2000 mg. If desired, this may be administered in divided doses 2 to 4 times a day in unit dosage form containing from about 125 mg to about 1000 mg or in sustained release form.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts. Such salt forms exhibit the same order of activity as the free base forms.

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets or capsules. The compounds may alternatively be administered topically in such conventional forms as ointments or creams. The concentration of the active substance in such topical application forms will of course vary depending on the compound employed, the treatment desired and the nature of the form etc. In general, however, satisfactory results are obtained at concentrations of from 0.05 to 3, in particular 0.1 to 1 wt %.

A compound with particularly interesting activity is the compound of Example 4.

One group of compounds has a formula Ig,

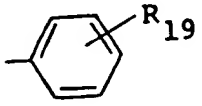


Ig

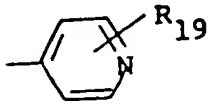
wherein R_1^I is 1-naphthyl, optionally mono-substituted by lower alkyl or alkoxy,

u is a whole number from 1 to 8,

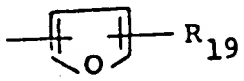
R_6^{II} is of formula



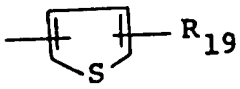
(a)



(b)



(c)



(d)

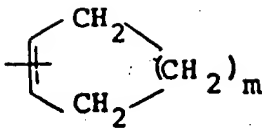
wherein R_{19} is hydrogen, hydroxy, lower alkoxy or lower alkyl,

or of formula

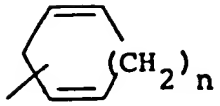
$$-CO-OR_{20} \qquad \text{(e)}$$

wherein R_{20} is alkyl (C_{1-12}) or phenylalkyl-(C_{7-12})

or of formula

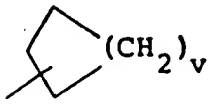


(f)



(g)

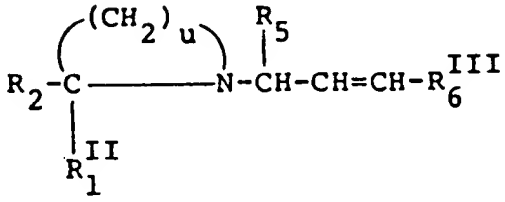
or



(h)

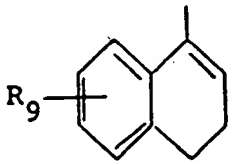
wherein m, n and v are as defined above.

Another group of compounds comprises those of formula Ih,



Ih

wherein R_1^{II} is a radical of formula IIa, IIb wherein X is oxygen or sulphur, IIc, IId wherein s is 4, IIe wherein t is 3 or a radical of formula



wherein R_9 is as defined above,

R_2 and R_5 are independently hydrogen or lower alkyl,

u is a whole number from 1 to 8,

R_6^{III} is as defined above for R_6,

with the following provisos,

(a) R_{10} is other than phenyl or phenylalkoxy, and

(b) when R_1^{II} is 1-naphthyl optionally mono-substituted by lower alkyl or alkoxy and R_2 and R_5 are each hydrogen, R_6^{III} is other than

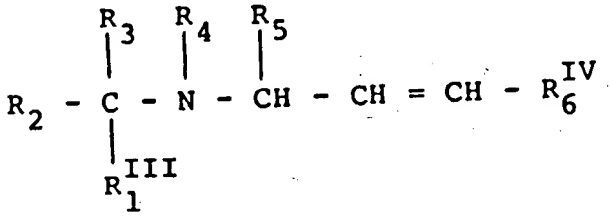
(i) a radical of formula IIIa, IIIb or IIIf,

(ii) a radical of formula IIIc, IIId or IIIe, wherein R_{11}, R_{12} and R_{13} are each hydrogen, or

(iii) a radical of formula IIIg wherein one of R_{17} and R_{18} is hydrogen and the other is hydroxy, lower alkyl or lower alkoxy, or

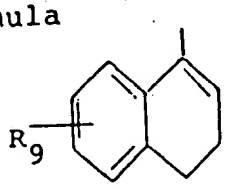
(iv) an optionally substituted thiophen or furan radical.

A further group of formula I compounds comprises compounds of formula Ii,



Ii

wherein R_1^{III} is a radical of formula IIa, IIb wherein X is oxygen or sulphur, IIc, IId wherein s is 4, IIe wherein t is 3, or a radical of formula



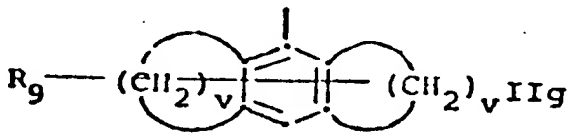
R_2, R_3, R_4, R_5 and R_9 are as defined above, with the proviso that R_3 and R_4 are other than $-(CH_2)_u-$,

R_6^{IV} is as defined above for R_6 with respect to formula I, with the following provisos

(i) R_{10} is other than phenyl or phenylalkoxy and

(ii) when R_1 is a radical of formula IIa, R_6^{IV} is other than a radical of formula IIIg, or phenyl.

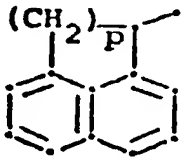
or



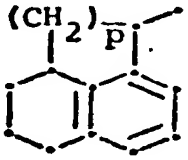
IIg

and R_2 represents hydrogen or lower alkyl,

or R_1 and R_2 together represent a group of formula



IIh



IIi

whereby in the formulae IIa to IIi,

R_7 and R_8 represent, independently, hydrogen, halogen, trifluoromethyl, hydroxy, nitro, lower alkyl or lower alkoxy,

R_9 represents hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy,

X represents oxygen, sulphur, imino, lower alkyl imino or a radical of formula $-(CH_2)_r-$,

p is 1, 2 or 3,

r is 1, 2 or 3,

s is 3, 4 or 5,

t is 2, 3 or 4, and

v is 3, 4, 5 or 6;

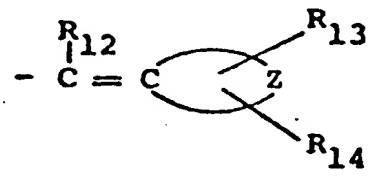
R_3 and R_5 represent, independently, hydrogen or lower alkyl, and

R_4 represents C_{1-6}alkyl or C_{3-8} cycloalkyl-(C_{1-6})-alkyl; and

R_6 represents a group of formula

$-C \equiv C - R_{11}$ IIIa $\quad - \underset{\underset{R_{11}}{|}}{C} = CH_2$ IIIb

or



IIIc

wherein R_{11} represents hydrogen, optionally α-hydroxy substituted alkyl; alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, phenyl, phenalkyl or thienyl,

R_{12}, R_{13} and R_{14} represent, independently, hydrogen or lower alkyl, and

represents a C_{5-8} cycloalkylidene radical optionally containing a double bond; or

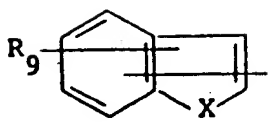
b) R_1 represents a group of formula IIa to IIg as defined under a),

R_2 represents hydrogen or lower alkyl,

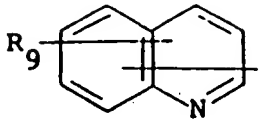
R_3 and R_4 together form a group $-(CH_2)_u-$, wherein u is an integer of 1 to 8, and

R_5 and R_6 have the meanings given under a).

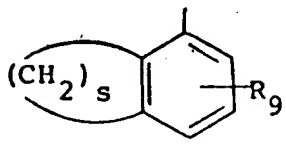
processes for their production, their use as pharmaceuticals and pharmaceutical compositions containing them.



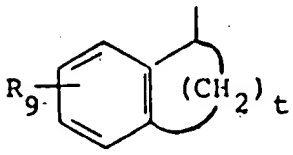
IIb



IIc



IId



IIe

wherein R_9 is hydrogen, halogen of atomic number from 9 to 53, hydroxy, lower alkyl or lower alkoxy,

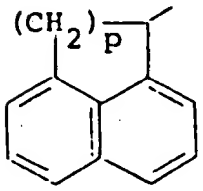
X is oxygen, sulphur, imino, lower alkylimino or a radical of formula $-(CH_2)_r-$ wherein r is 1, 2 or 3,

s is 3, 4 or 5, and

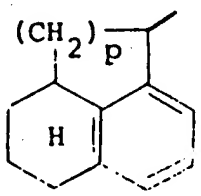
t is 2, 3 or 4, and

R_2 is hydrogen or lower alkyl, or

(ii) R_1 and R_2 together with the carbon atom to which they are bound form a radical of formula IIf or IIg,



IIf



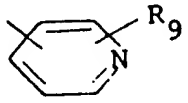
IIg

wherein p is 1, 2 or 3,

R_3 and R_5, independently, are hydrogen or lower alkyl,

R_4 is alkyl (C_{1-6}), alkenyl (C_{3-12}), alkynyl (C_{3-12}) or cycloalkyl (C_{3-8})-alkyl (C_{1-6}); and

R_6 is (i) an aromatic, five-membered heterocycle containing one oxygen, sulphur or nitrogen hetero-ring atom and optionally an additional one or two nitrogen hetero-ring atoms and being optionally substituted on a carbon ring atom by halogen of atomic number from 9 to 53, hydroxy, lower alkyl or lower alkoxy, and any nitrogen ring atom present being optionally substituted when possible, by lower alkyl, (ii) a radical of formula IIIa,



IIIa

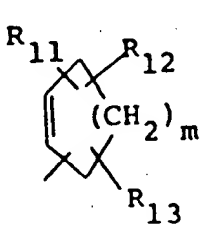
wherein R_9 is as defined above,

(iii) a radical of formula IIIb,

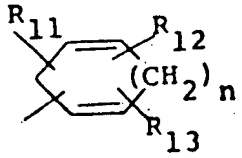
$$-CO-R_{10} \qquad \text{IIIb}$$

wherein R_{10} is alkyl (C_{1-12}), alkenyl (C_{3-12}), alkynyl (C_{3-12}) cycloalkyl (C_{3-8})-alkyl (C_{1-6}), phenyl-alkyl (C_{7-12}), phenyl, phenylalkoxy (C_{7-16}), or amino-alkyl (C_{1-12});

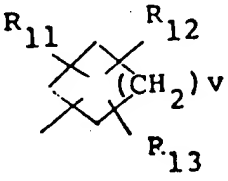
(iv) a radical of formula IIIc, IIId or IIIe,



IIIc



IIId



IIIe

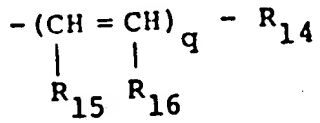
wherein R_{11}, R_{12} and R_{13}, independently, are hydrogen or lower alkyl,

m is a whole number from 0 to 4,

n is a whole number from 0 to 3, and

v is a whole number from 0 to 5,

(v) a radical of formula IIIf,

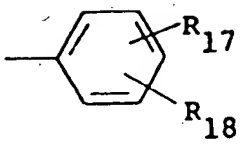


wherein R_{14} is lower alkyl, alkoxy (C_{1-12})-carbonyl, alkenyl (C_{3-12}), alkynyl (C_{3-12}), phenylalkyl (C_{7-12}) or phenyl,

R_{15} and R_{16}, independently, are hydrogen or lower alkyl, and

q is a whole number from 0 to 5, or

(vi) a radical of formula IIIg



IIIg

wherein R_{17} and R_{18}, independently, are hydrogen, halogen of atomic number from 9 to 53, trifluoromethyl, hydroxy, nitro, lower alkyl or lower alkoxy, with the proviso that one of R_{17} and R_{18} is other than hydrogen, and with the general proviso that R_1 is not a radical of formula IIa when R_6 is a radical of formula IIIg or phenyl, R_2 is hydrogen and R_3 is hydrogen or lower alkyl,

b) R_1 is a radical of formula IIa to IIe, as defined above,

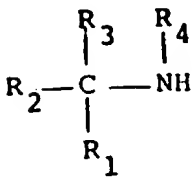
R_2, R_5 and R_6 are as defined above, and

R_3 and R_4 together are $-(CH_2)_u-$ wherein u is a whole number from 1 to 8,

or an acid addition salt thereof.

2. A process for the production of a compound as claimed in Claim 1, which comprises

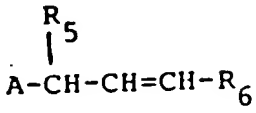
a) reacting a compound of formula IV,



IV

wherein R_1 to R_4 are as defined above,

with a compound of formula V,

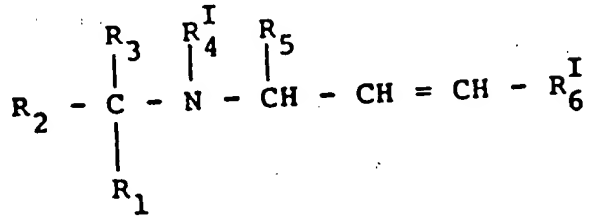


V

wherein A is a leaving group, and

R_5 and R_6 are as defined above, or

b) producing a compound of formula Ia,

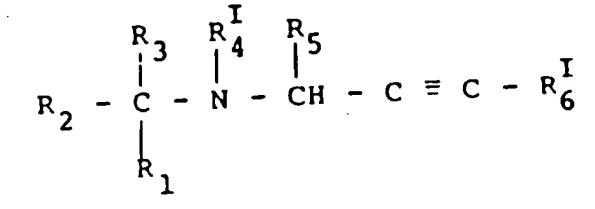


Ia

wherein R_1 to R_3 and R_5 are as defined above, and

R_4^I and R_6^I are as defined above for R_4 and R_6 respectively, with the proviso that they each are other than alkynyl,

by reducing a compound of formula VI,

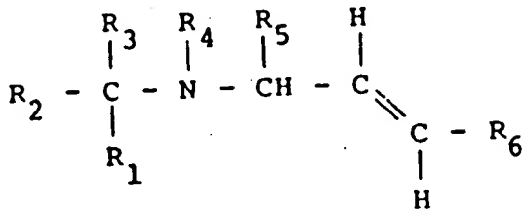


VI

wherein R_1 to R_3, R_4^I, R_5 and R_6^I are as defined above,

or

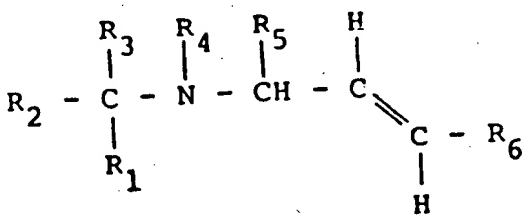
c) producing a compound of formula Ib,



Ib

wherein R_1 to R_6 are as defined above,

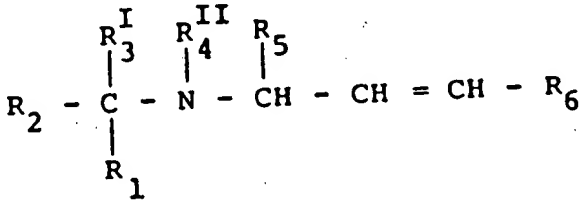
by isomerising photochemically a compound of formula Ic,



Ic

wherein R_1 to R_6 are as defined above, or

d) producing a compound of formula Id,



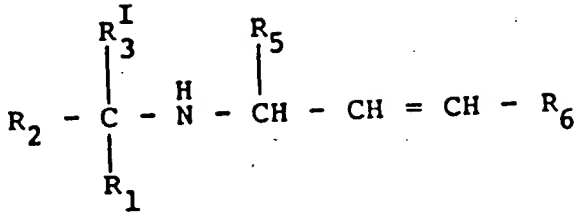
Id

wherein R_1, R_2, R_5 and R_6 are as defined above,

R_3^I is hydrogen or lower alkyl,

R_4^{II} is alkyl(C_{1-6}), alkenyl(C_{3-12}), alkynyl (C_{3-12}) or cycloalkyl(C_{3-8})alkyl(C_{1-6});

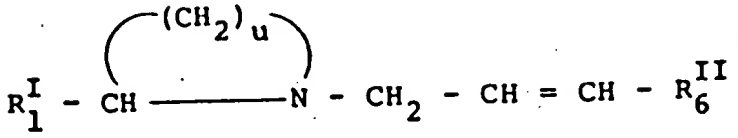
by introducing the group R_4^{II} into a compound of formula VII,



VII

wherein R_1, R_2, R_3^I, R_5 and R_6 are as defined above.

3. A compound of Claim 1, having the formula Ig,

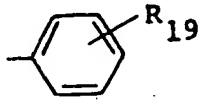


Ig

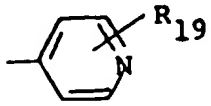
wherein R_1^I is 1-naphthyl, optionally mono-substituted by lower alkyl or alkoxy,

u is a whole number from 1 to 8,

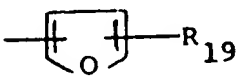
R_6^{II} is of formula



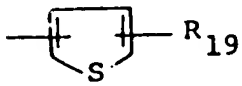
(a)



(b)



(c)



(d)

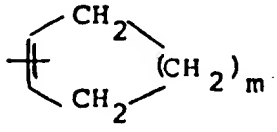
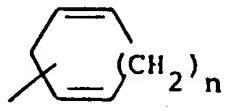
wherein R_{19} is hydrogen, hydroxy, lower alkoxy or lower alkyl,

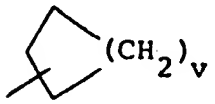
or of formula

$$-CO-OR_{20} \qquad (e)$$

wherein R_{20} is alkyl (C_{1-12}) or phenylalkyl-(C_{7-12})

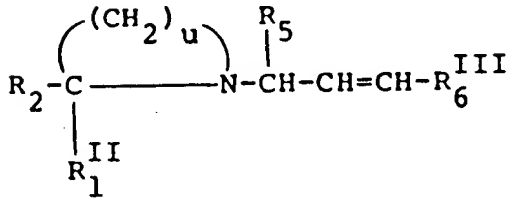
or of formula

 (f)  (g)

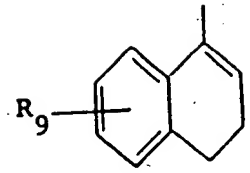
or  (h)

wherein m, n and v are as defined in Claim 1.

4. A compound of Claim 1, having the formula Ih,

 Ih

wherein R_1^{II} is a radical of formula IIa, IIb wherein X is oxygen or sulphur, IIc, IId wherein s is 4, IIe wherein t is 3 or a radical of formula



wherein R_9 is as defined in Claim 1,

R_2 and R_5 are independently hydrogen or lower alkyl,

u is a whole number from 1 to 8,

R_6^{III} is as defined in Claim 1 for R_6,

with the following provisos,

(a) R_{10} is other than phenyl or phenylalkoxy, and

(b) when R_1^{II} is 1-naphthyl optionally mono-substituted by lower alkyl or alkoxy and R_2 and R_5 are each hydrogen, R_6^{III} is other than

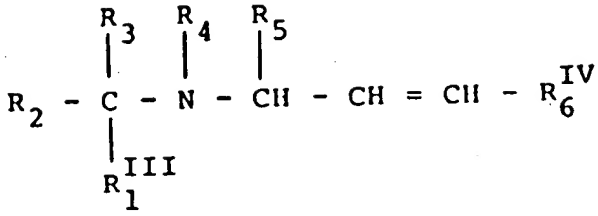
(i) a radical of formula IIIa, IIIb or IIIf,

(ii) a radical of formula IIIc, IIId or IIIe, wherein R_{11}, R_{12} and R_{13} are each hydrogen, or

(iii) a radical of formula IIIg wherein one of R_{17} and R_{18} is hydrogen and the other is hydroxy, lower alkyl or lower alkoxy, or

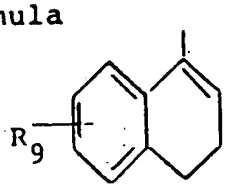
(iv) an optionally substituted thiophen or furan radical.

5. A compound of Claim 1 having the formula Ii,



Ii

wherein R_1^{III} is a radical of formula IIa, IIb wherein X is oxygen or sulphur, IIc, IId wherein s is 4, IIe wherein t is 3, or a radical of formula



R_2, R_3, R_4, R_5 and R_9 are as defined in Claim 1, with the proviso that R_3 and R_4 are other than $-(CH_2)_u-$,

R_6^{IV} is as defined in Claim 1 for R_6 with respect to formula I, with the following provisos

(i) R_{10} is other than phenyl or phenylalkoxy and

(ii) when R_1 is a radical of formula IIa, R_6^{IV} is other than a radical of formula IIIg, or phenyl.

6. A compound of Claim 1 which is N-(3-cyclohexyl-2-trans-propenyl)-N-methyl-N-(1-naphthylmethyl)amine.

7. A pharmaceutical composition comprising a compound of any one of Claims 1, and 3 to 6 in free base form or in chemotherapeutically acceptable acid addition salt form in association with a chemotherapeutically acceptable diluent or carrier.

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